are there, Blumenthal said; it's just a matter of knowing where and how to find them. But Schardt defended the desire to reproduce such studies in U.S. labs, pointing out that, for example, European studies on the efficacy of St. John's wort for treating depression average a length of only five weeks—even though St. John's wort can take as long as four weeks to have any effect. He also asserted that the results of certain studies may not be as compelling as some claim. For instance, in response to a claim that some 28 controlled trials of various forms of echinacea have been conducted in Europe, Schardt said that most of those studies used parenteral echinacea, which is not available in the United States, or proprietary products that also are not available to U.S. consumers. Furthermore, Schardt said, the results of several controlled trials testing the effects of oral echinacea supplements on the common cold and influenza are inconclusive. Still, there was general agreement among the participants that the United States must display more willingness to cooperate with and participate in international research on standardization, efficacy, and safety.

Financial support. Many speakers felt that the money for testing, analyzing, and evaluating the published safety and efficacy data on medicinal herbs should come from the government, and looked to the FDA as the natural choice for initiating such studies. But Yuan-Yuan Chiu, deputy director of the Office of New Drug Chemistry at the FDA Center for Drug Evaluation and Research, claimed the agency has barely enough resources to maintain the programs already in place, and called on the other government agencies represented to share their funds and resources.

Others felt that industry bears the burden of responsibility for supporting research. Pharmaceutical companies routinely spend 10–20% of their profits on research and development, a figure that is not borne out in the botanical industry. But, said Loren Israelsen, executive director of the Utah Natural Products Alliance, contrary to an editorial in the 17 September 1998 issue of the *New England Journal of Medicine* in which editors Marcia Angell and Jerome Kassirer suggest the botanical industry is not interested in research, the industry very much wants to conduct and collaborate on botanicals research.

Israelsen described some of the dilemmas faced by the industry in terms of research incentives versus expenditures. In order to receive FDA approval as a nonprescription drug, each substance within a given plant—not just those within the extract used in the botanical preparation—would need to be studied in a lengthy, expensive process. In addition, the FDA review process for nonprescription drugs does not allow consideration of foreign data. Therefore, many studies that have already been done overseas would need to be duplicated.

Another issue is the Dietary Supplement Health and Education Act of 1994, which for the first time allowed botanical manufacturers to label their products with claims of how the product may affect the structure or functioning of the body. With the passage of the act, many manufacturers began conducting legitimate research in order to formulate their claims, but some manufacturers indulge in "borrowed science"—applying the results of another company's studies to their own products, often leading to inaccurate claims (the resultant mislabeling is addressed under the Federal Food, Drug, and Cosmetic Act). Finally, most synthetic drugs are developed with the goal of being patented. But with the countless varieties of botanical products being sold, it is impossible to claim market exclusivity as a research incentive.

Botanicals Today . . . and Tomorrow

Research and regulatory decisions are much too complex to base on a single workshop. However, most participants seemed satisfied to have been able to voice the concerns of their particular camps, and excited about the evident—albeit fragmented—wealth of expertise represented at the workshop. A summary of several recommendations drawn from workshop presentations and discussions is being compiled by the NIEHS. Of the workshop, co-organizer H.B. Matthews said, "We've certainly set the stage for a continuing dialogue on this subject."

According to Israelsen, a "broad understanding among all interested parties of the issues involved" is needed. "We need to serve the consumer, set aside animosities, and just do the work," he said. "The real [goal] is that the consumers have safe botanical products.

Autoimmune Disease and the Environment

According to a study published in the September 1997 issue of *Clinical Immunology and Immunopathology* by scientists at The Johns Hopkins University in Baltimore, Maryland, at least 10 million people in the United States are affected by one of 80 known autoimmune diseases. These diseases include both organ-specific conditions, such as type I diabetes, and system-wide diseases, such as systemic lupus erythematosus. They range from the well-known, such as multiple sclerosis, to the relatively rare and obscure, such as Takayasu's arteritis (which attacks the aorta and its branches). Perhaps because of the wide range of the health effects caused by these diseases, little is known about their origin and epidemiology.

In an effort to address the dearth of etiologic information on this mysterious family of diseases, a workshop entitled Linking Environmental Agents and Autoimmune Diseases was held 1–3 September 1998 at the NIEHS campus in Research Triangle Park, North Carolina. The workshop was jointly sponsored by the NIEHS, the EPA National Health and Environmental Effects Research Laboratory (NHEERL), the NIH Office of Rare Diseases, the NIH Office of Research on Women's Health, the National Institute of Allergy and Infectious Disease, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Arthritis, Musculoskeletal, and Skin Diseases, the American Autoimmune Related Diseases Association, and the Juvenile Diabetes Foundation.

Almost all autoimmune diseases occur more often in women than in men; in some of these diseases, more than 90% of patients are female. It is not clear exactly why women are targeted more often than men, but estrogen is suspected to play a pivotal role. Autoimmune diseases seem to particularly attack connective tissue and the neuromuscular, endocrine, and gastrointestinal systems, but are not unknown in other parts of the body.

Autoimmunity occurs when the body's immune system turns against itself. The immune system is designed to protect the body by producing antibodies in response to invading microorganisms such as viruses or bacteria. Sometimes, for reasons that are still not fully understood, these antibodies are directed against self-, rather than foreign, antigens. Such a response probably occurs naturally in most peop le to some extent, but for someone with a genetic predisposition to autoimmune disease, bacteria, viruses, toxic agents, or certain drugs may provide the boost necessary to trigger a full-fledged autoimmune response. Other factors that are believed to influence the development of autoimmune disease include age, gender, and reproductive status (e.g., pregnancy).

The workshop drew over 100 scientists from a variety of disciplines, serving as a forum for immunologists, developmental biologists, autoimmune specialists, epidemiologists, molecular biologists, and toxicologists to define the state of the science, identify data gaps, and map out the research still

needed to fully understand the mechanistic and causative links between environmental agents and the various forms of autoimmune disease. Says Jerrold Heindel, a program administrator in the NIEHS Organs and Systems Toxicology Branch, "This was the first time that this kind of broad group ever got together [to discuss autoimmune disease]." Heindel says the workshop allowed for a stimulating exchange of ideas and perspectives as representatives from diverse fields compared their perceptions of the problems that need to be addressed in order to move ahead with research.

"A major aim of the workshop was to look for common threads that would make it easier to define the mechanism of autoimmune diseases and the role of environmental agents," says Heindel. "No significant common threads were noted [at the workshop], which means that we still have to examine each disease individually, which makes for a much bigger problem. We still hope that, as more data are accumulated, common threads will appear."

Perhaps the most pressing need identified at the workshop is for a nationwide surveillance system to establish the occurrence of autoimmune disease. Such a system would also help identify clusters that might be associated with a particular environmental exposure, cohorts for study, and susceptible populations. Dori Germolec, a group leader of the NIEHS Environmental Immunology Laboratory, says, "Many people agreed we need a better nationwide registry for autoimmune diseases, both the specific diseases themselves and autoimmune diseases as a whole."

Genetic factors have been shown to play a role in the development of autoimmune diseases. For example, in a review article published in the 3 May 1996 issue of *Cell*, Timothy J. Vyse of the National Jewish Center for Respiratory Medicine and Immunology in Denver, Colorado, and John A. Todd of the Wellcome Trust Centre for Human Genetics in Oxford, United Kingdom, used maps of markers covering the mouse, rat, and human genomes to identify 38 genes that predispose humans and experimental animals to autoimmune disorders. But, as Glinda Cooper, an epidemiologist with the NIEHS Environmental Diseases and Medicine Program, pointed out at the workshop, that does not negate the possible role of environmental agents in the initiation or exacerbation of disease. "It's not [a matter of] 'genetics versus environment,'" she says. "As researchers, our goal is to understand the interaction between genes and the environment."

A palette of environmental factors have been posited as possibly triggering various autoimmune disorders. For instance, exposure to chemicals such as dioxins and polychlorinated biphenyls has been linked with non-Hodgkin's lymphoma, while certain dietary factors seem to contribute to type 1 diabetes. Other environmental suspects include ultraviolet radiation (multiple sclerosis), cross-reactivity with environmental antigens (type 1 diabetes), ionizing radiation (systemic lupus erythematosus), stress (rheumatoid arthritis), and exposure to heavy metals such as lead and mercury (autoimmune glomerulonephritis).

There is also a need, said workshop participants, to develop and identify research tools such as biomarkers of disease that are amenable to both animal and human studies, questionnaires for epidemiologic and clinical tests, and testing strategies to screen chemicals for the potential to initiate or exacerbate autoimmune disease. In an article published in the March 1995 issue of *Immunology Today*, Argyrios N. Theofilopoulos, an immunologist at the Scripps Research Institute in La Jolla, California, predicted that "the definition of [autoimmune] diseases is about to be revolutionized by the development of genome scanning approaches, such as dense chromosomal maps based on polymorphic microsatellite DNA and other informative markers."

The findings of the breakout groups will be compiled into a list of research recommendations that will be distributed to NIH institutes, interested foundations, and the research community. Says Mary Jane Selgrade, chief of the Immunotoxicology Branch at the NHEERL, "It is our hope that the data gaps and needs the workshop participants have identified will stimulate research into the next decade."

Talk of the Towns

In the belief that dialogue is the first step to resolving the environmental problems society currently faces, the NIEHS has instituted a series of regional town meetings to be hosted by various NIEHS Environmental Health Sciences Centers. These meetings are aimed at giving a voice to the myriad groups (including local, state, and federal health officials, policy makers, academicians, and members of the community) interested in public health and the environment.

The first town meeting was held 17–18 September 1998 and was hosted by the Environmental and Occupational Health Sciences Institute, a program of the University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School and Rutgers University. This event set the goals for the planned series of town meetings. The primary goal is to provide a platform for open dialogue to encourage better coordination among the health professionals working on community exposures, industrial exposures and pesticides, site-specific exposures and cluster issues, and other environmental issues that impact human health. A secondary goal is to promote local and state media coverage of environmental health to broaden public understanding.

Three more town meetings (listed below) are currently scheduled around the United States, and more are planned for later in 1999.

19–20 January 1999
"Preventing Environmental Disease: Barriers and Solutions"
Cincinnati Museum Center
Cincinnati, Ohio
Contact: 513-558-5439

19 February 1999 (date tentative)
"Disease End Points in Children"
University of California at Berkeley
Berkeley, California
Contact: 510-643-9815